REVIEW

Vaccination strategies to enhance immunity in neonates

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Neonates are particularly susceptible to infection. This vulnerability occurs despite their responsiveness to most vaccines. However, current vaccines do not target the pathogens responsible for most of the severe neonatal infections, and the time it takes to induce protective pathogen-specific immunity after vaccination limits protection in the first days to weeks of life. Alternative strategies include using vaccines to broadly stimulate neonatal immunity in a pathogen-agnostic fashion or vaccinating women during pregnancy to induce protective antibodies that are vertically transferred to offspring within their window of vulnerability. Protection may be further improved by integrating these approaches, namely vaccinating the neonate under the cover of vertically transferred maternal immunity. The rationale for and knowledge gaps related to each of these alternatives are discussed.

Infectious morbidity and mortality are highest in the first weeks after birth (*1*, *2*). This vulnerability is not unexpected, given the predominantly naïve phenotype of neonatal immune cells and distinctive immunological challenges at birth, which require discrimination between not only innocuous self-antigens and noninherited maternal antigens but also the wide assortment of foreign antigens associated with primary commensal colonization (*3*, *4*). Susceptibility to severe infection likely reflects a combination of these physiological constraints.

Vaccination remains one of the most cost-effective ways of preventing infection. Vaccines against poliomyelitis, hepatitis B, tuberculosis, tetanus, pertussis, diphtheria, *Haemophilus influenzae* type b (Hib), rotavirus, and measles are administered to millions of infants, preventing an estimated 2.5 million deaths each year (*5*). Although vaccination has clearly benefited older infants and children, it has been considerably less effective in the first month of life (*1*, *2*). The World Health Organization recommends vaccination against tuberculosis, hepatitis B, and polio as soon as possible after birth (<24 hours) to accelerate priming of protective immune components. Likewise, maternal vaccination protects against infection by certain pathogens through vertically transferred immunity (*6*). However, emerging evidence shows that neonatal infections in lower- and middle-income regions are caused by a diversity of pathogens (Fig. 1). A recent meta-analysis identified *Staphylococcus aureus*, *Klebsiella*, and *Escherichia coli* spp. as the dominant causes of bacteremia and sepsis in neonates (infants younger than 28 days) in sub-Saharan Africa (*7*). *Ureaplasma* spp. and Group B *Streptococcus* were most frequently identified among cases of suspected early onset sepsis (infants 3 days or younger) in South Africa (*8*), whereas respiratory syncytial virus (RSV) and *Ureaplasma* spp. were the most commonly identified pathogens in cases of possible serious bacterial infection in infants younger than 60 days in Southeast Asia (*9*). Notably, none of these pathogens are covered by vaccines currently in clinical use (Fig. 1). Furthermore, the inciting pathogen was not identified in >70% of cases of clinically suspected infection, despite the use of cutting-edge diagnostic approaches (*8*, *9*). Although some of these undiagnosed cases may not be bona fide infections, the proportion of causative pathogens missed by vaccination is still likely to be greater than currently appreciated. Thus, alternative strategies to enhance early life immunity against a wide variety of pathogens are needed. We summarize the principles underpinning vaccination of neonates and their mothers, including increasingly recognized pathogen-agnostic benefits, which highlight the need to consider the mother–newborn dyad as one immunological unit to optimally enhance early life immunity.

Pathogen-specific immunity after neonatal vaccination

The neonate is often inappropriately considered "immature" and therefore presumed unable to respond to vaccination. Dampened antibody responses to T cell–independent polysaccharide antigens of encapsulated bacterial pathogens, including Hib and pneumococcus, until 2 years of age correlate with reduced marginal-zone B cells. Nonetheless, the conjugation to protein carriers activates T cells, resulting in robust protective antibody responses even in neonates (*10*). Similarly, diphtheria–tetanus–whole cell pertussis and some acellular pertussis vaccine formulations have been described to elicit reduced responses in neonates compared with older infants (*11*). However, monovalent acellular pertussis vaccines administered to neonates induce strong primary responses and do not induce tolerance to vaccine boosters (*12*). Compared with older infants, neonates are just as, if not more, responsive to vaccines currently included in neonatal immunization programs, namely bacillus Calmette-Guérin (BCG) vaccine, oral polio vaccine (OPV), and hepatitis B vaccine (*13*, *14*). The serological response of the neonate is also robust in response to other vaccines not currently licensed for neonatal administration, for example, those targeting rotavirus, diphtheria, and tetanus (*10*).

Even live vaccines have an outstanding safety record in neonates. Disseminated BCG infection is exceptionally rare (<1 per one million vaccine recipients) and almost exclusively occurs in infants with underlying immune deficiency (*15*). Vaccine-associated polio primarily occurs in underimmunized populations, which facilitate person-to-person spread, persistence, and eventual reversion into a more virulent phenotype. Vaccine-associated polio is expected to further decline with reformulation of trivalent to bivalent OPV (*16*). Furthermore, evidence of similar rates of infection by non–vaccine-targeted pathogens in older children regardless of prior cumulative vaccine exposure argues against the misconception that vaccines may overload and weaken the immune system (*17*). Thus, neonates are exceedingly capable of responding robustly and safely to most vaccines.

Given that neonates are capable of robust vaccine responses, why have current vaccination programs not lead to mortality reductions in neonates that are comparable to those in older infants and children? First, current vaccines administered to neonates do not specifically target the pathogens that cause severe infection in the first weeks of life (Fig. 1). Although tuberculosis, hepatitis B, and polio can be acquired within the first weeks after birth, these infections clinically manifest mostly outside of the neonatal period. For pathogens that do cause severe infection in the first weeks after birth, such as RSV, *Ureaplasma*, and several other bacteria, vaccines are either unavailable or have not yet been tested in neonates. Second, priming a protective adaptive immune response in predominantly naïve neonatal cells often takes weeks (*18*), whereas infections can cause morbidity and mortality within the first few days after birth (*1*, *2*) (Fig. 2A). This discordance between when infections occur and the time it takes to prime protective pathogen-specific immunity makes strategies aimed at inducing protective neonatal adaptive immune components challenging. To more effectively protect against infections manifesting in the neonatal period, alternative strategies, such as boosting resistance through non–pathogen-specific (i.e., pathogen-agnostic) approaches

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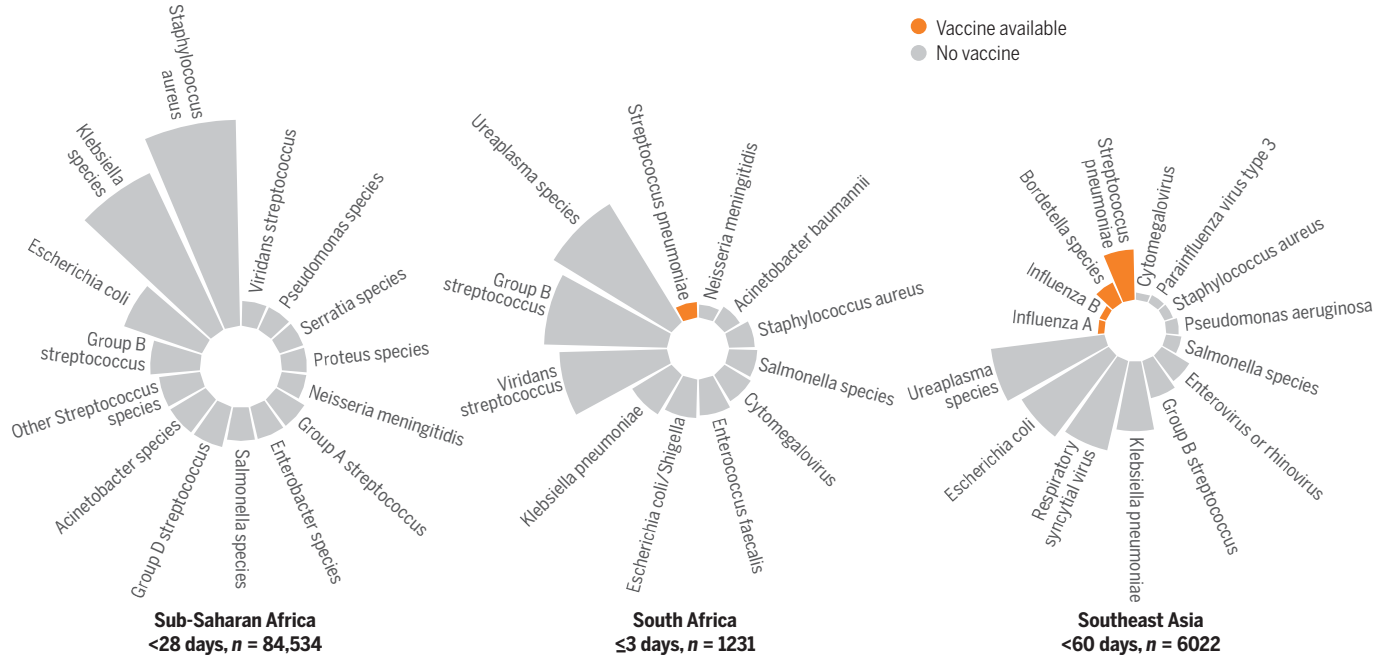

Fig. 1. Current maternal and neonatal vaccines do not cover most pathogens associated with severe infection in early life. Relative proportion of each pathogen, represented by the size of each segment, identified in recent studies of suspected sepsis in early life (*7*–*9*). The top pathogens from each study are shown, covering >90% of cases in which a pathogen was identified. Age range (in days) and number of neonates are shown for each study.

and/or promoting transfer of pathogen-specific maternal immunity, must be considered.

Pathogen-agnostic protection after neonatal vaccination

Accumulating evidence shows that live vaccines can broadly enhance host resilience against infection beyond their specific pathogen target (*19*, *20*). A recent meta-analysis encompassing >6000 low–birth weight neonates attributed an additional 38% reduction in neonatal mortality to BCG vaccine administered at birth, beyond protection against tuberculosis (*21*). A separate study including >7000 neonates showed a 40% reduction in mortality when OPV was administered with BCG vaccine within the first 2 days of life (*22*). These pathogen-agnostic protective effects appear to be fast-acting, because substantial reduction in overall neonatal mortality can be identified within the first 3 days after BCG vaccine administration (*21*), in contrast to the weeks required to achieve pathogen-specific immunity. Enhanced serological responsiveness to other vaccines in neonates administered BCG vaccine at birth further highlights the broad immunostimulatory effects of BCG vaccination (*23*).

Mechanisms by which live vaccines confer pathogen-agnostic protective effects have not been established, but they likely include cross-reactive T cells (e.g., heterologous immunity) or activation of innate immune components (e.g., trained immunity) (*19*, *20*). Another unresolved question is whether pathogen-agnostic protective effects primed by live vaccines are restricted to the neonatal period. Analysis of >15,000 children in rural Guinea-Bissau showed that mortality reductions associated with BCG vaccine scarring were limited to children vaccinated within the first 4 weeks of life, with the most pronounced effect observed among those vaccinated within the first week of life (*24*). Although a distinctive window of opportunity in the neonatal period could be inferred from these data, this pathogen-agnostic protection has also been shown for older infants administered other live vaccines (*25*, *26*). An expanded window of plasticity for pathogen-agnostic immunity is supported by similar reductions in childhood mortality associated with live attenuated measles vaccine administered after 4 months of age (*27*). Given that pathogen-agnostic approaches have the potential to confer broad and fast protection to the neonate—bypassing each of the drawbacks associated with current pathogen-specific strategies for neonatal immunization—establishing protective mechanisms is an important next step.

Pathogen-specific immunity after vaccinating mothers

Multiple adaptations occur during pregnancy to accommodate growth and avert rejection of the semiallogeneic fetus. These tolerogenic adaptations are likely anatomically confined and/or restricted to cells with fetal specificity, because the response to vaccines administered during pregnancy is largely comparable to that of nonpregnant women (*28*). Vertically transferred maternal antibodies protect offspring in the early postnatal period (*6*). An important distinction between vaccination of mothers and neonatal immunization is the transient nature of the protective benefits conferred by non-self-renewing antibodies that functionally persist in infants only for several months, thereby deferring infection until the consequences are less severe (Fig. 2B).

Vaccination during pregnancy has already been shown to be effective for several important pathogens. For example, tetanus vaccination of pregnant women reduces neonatal mortality from tetanus by >90% (*29*). Protection of infants against respiratory illness and confirmed influenza infection ranges from 30 to 60% when mothers are vaccinated during pregnancy (*30*). Protective efficacy against pertussis in the first 2 to 3 months of life is ~90% after maternal vaccination (*31*). In light of these considerable benefits, developing vaccines for pregnant women that target other neonatal pathogens should be prioritized.

Maternal antibodies transferred across the placenta are almost exclusively immunoglobulin G (IgG), the levels of which exponentially increase in fetal tissues during the final weeks of gestation. Transfer is coordinated by binding to Fc receptors expressed by trophoblasts, macrophages, and endothelial cells, with preferential transfer of some isotypes (*32*). The accelerated transfer of maternal antibodies in later gestation means that immunity primed by maternal vaccination is drastically different for preterm infants. IgG levels are also reduced among small-for-gestational-age infants, as well as infants born to mothers with chronic infections, such as HIV or placental malaria (*33*). Maternal IgA and IgG antibodies are also transferred through

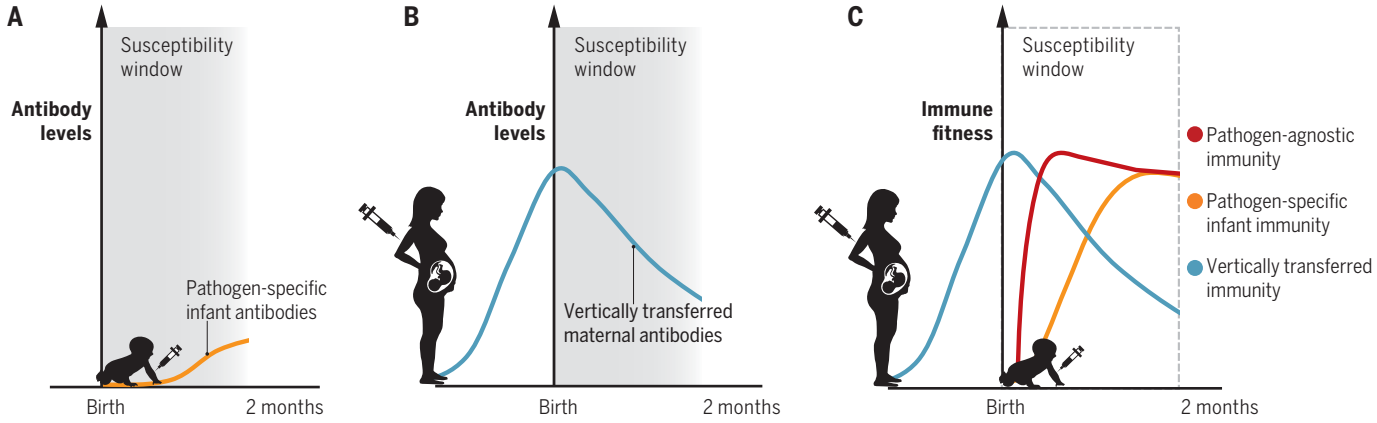

Fig. 2. Tempo of immunity provided by vaccination at birth compared with vaccination during pregnancy in relation to the neonatal window of infection susceptibility. (**A**) Antibody levels primed by neonatal vaccination increase with delayed tempo, which offers suboptimal protection during the early life window of susceptibility. (**B**) Maternal immunization provides high levels of pathogen-specific antibodies at birth and is an effective strategy for narrowing the window of susceptibility to specific pathogens. (**C**) Combining maternal vaccination with pathogen-agnostic and pathogen-specific benefits of neonatal vaccination may contribute equally to optimal neonatal immune fitness and efficiently close the early life window of susceptibility.

breastfeeding, and increased levels of both isotypes can be detected in breastmilk after vaccination during pregnancy (*28*). Optimal protection of neonates will require establishing the molecular determinants of antibodies transferred through breastmilk and whether they functionally complement placentally transferred antibodies.

Although vaccination during pregnancy raises concerns regarding safety, the vaccines currently administered to pregnant women have excellent safety profiles. There is no evidence of increased pregnancy complications with inactivated vaccines adjuvanted with alum or oil-based emulsions (*34*). Live attenuated vaccines, however, are currently not recommended during pregnancy. Nonetheless, analysis after their inadvertent administration suggests that they are safe. Rubella virus vaccine administration to >3500 pregnant women with documented serological susceptibility did not cause congenital rubella syndrome, and only one case of asymptomatic virus shedding was reported (*35*). Administration of OPV or yellow fever vaccine in outbreak settings did not cause increased rates of growth retardation, congenital anomalies, or pregnancy complications in women vaccinated during pregnancy (*34*). One potential exception is smallpox vaccination; But even in this case, the largest meta-analysis (including >12,000 pregnant women) showed only marginally increased (relative risk: 1.3) incidence of congenital defects, with a similar incidence of other complications, including spontaneous abortion, stillbirth, and preterm birth (*36*). Thus, most live vaccines appear to be safe during pregnancy.

Linking the mother–newborn dyad

Chronic maternal infection with a variety of pathogens can affect infant health independently from pathogen transmission (*37*), along with the tempo and quality of immune development (*38*). HIV-exposed but uninfected infants have reduced levels of maternal antibodies and show increased susceptibility to severe infection by unrelated pathogens compared with infants not exposed to HIV (*39*). Cord blood cells from neonates born to mothers with chronic hepatitis B virus infection produce increased antimicrobial cytokines after stimulation with various bacterial pathogens (*40*). These phenotypic changes in neonatal immune cells may reflect stimulation by antigens transferred in utero, with evidence of both activating and tolerogenic impacts on fetal immune components (*41*, *42*). Maternal programming of neonatal immunity also persists after birth by way of cells, cytokines, and antibodies acquired through breastfeeding (*43*) and by maternal cells that establish microchimerism (*44*). Thus, immune fitness, defined as resistance to severe infection, is dominantly influenced by maternal immunological experience.

Vertical transfer of maternal antibodies is teleologically conserved, and enriched for glycosylated antibodies that promote antimicrobial activity in neonates (*6*, *32*, *33*, *45*). Vertically transferred immunity can also dominantly influence the response of offspring to vaccination. High-titer maternal antibodies have often been associated with diminished primary antibody response of infants to vaccines (*46*, *47*). A classical study prompted by increased symptomatic measles infection among children immunized before their first birthday showed a muted serological response in children with high-titer pre-vaccination antibodies and increased responsiveness in children with reduced pre-vaccine titers (*48*). Interference of infant serological response is also observed for other live and inactivated vaccines, although the reduction magnitude is variable between studies and individual vaccines (*33*, *49*, *50*).

Interference by preexisting antibodies is not specific to infants and instead likely reflects control of excessive antibody production classically described in adults (*51*). Masking of immunodominant epitopes, regulation of B cell activation and germinal center maturation, and B cell inhibition through FcγRIIB cross-linking are potential mechanisms (*52*, *53*). The priming of memory B cells is much less sensitive to the presence of high titers of preexisting antibodies, because infant responses to vaccine boosters are consistently preserved with primary vaccination under the cover of high titers of maternal antibodies (*54*–*56*). T cell priming also appears to be intact, because the presence of antibodies affects neither proliferation nor effector cytokine production (*57*, *58*). Thus, interference is generally restricted to the primary serological response of offspring to vaccination. However, the clinical implications remain uncertain, because memory B and T cell responses primed by vaccination of neonates under the cover of maternal immunity remain intact.

Vaccination during early infancy under the cover of maternal immunity may in fact prime responses that are more protective, especially considering the aforementioned pathogen-agnostic protective benefits of live vaccines. A 78% reduction in mortality was shown for infants administered live attenuated measles vaccine at 4.5 months of age in the presence of maternal measles antibodies at the time of vaccination (*27*). The reduction of infant mortality associated with BCG vaccination in the neonatal period is further enhanced among infants born to mothers with prior BCG priming (*59*). A more balanced response by vertically transferred innate and adaptive maternal factors including antibodies, cytokines, cells, or metabolites likely explains these enhanced protective benefits. Considering this potential to enhance antimicrobial host defense, further narrowing the window of neonatal susceptibility against a wide range of pathogens will likely require

stimulating pathogen-agnostic and pathogen-specific immunity by neonatal immunization under the cover of maternal immunity (Fig. 2C).

Outlook

Neonatal infection is a complex, multifaceted problem with many critical dimensions yet to be defined. The pathogens associated with neonatal infections in low-to-middle income areas have only recently been systemically evaluated using modern diagnostic tools (*8*, *9*) (Fig. 1). The wide range of identified bacteria and viruses with varying virulence, combined with the large fraction of cases where a specific pathogen was not identified, suggests that complex immunological perturbations in the neonatal period drive clinical sepsis. Future diagnostic and treatment strategies will need to go beyond current approaches, which are narrowly focused on specific inciting pathogens. Likewise, designing vaccines that target the mother–newborn dyad implies knowledge of how mother and child are immunologically linked. However, current knowledge of how human pregnancy is sustained remains rudimentary. The necessity for specific molecules and immune cell subsets in maintaining maternal–fetal tolerance has almost exclusively been established using preclinical pregnancy models (rodents), which do not recapitulate the more prolonged gestational length and in utero accumulation of fetal adaptive immune components observed in humans (*60*).

Despite our present ignorance, vaccines that prime pathogen-specific immunity in the maternal–fetal dyad clearly work. We are on the brink of eradicating poliomyelitis with vaccines administered to neonates. Eliminating neonatal tetanus is also within reach by way of maternal vaccination. Boosted pathogen-agnostic immunity primed by live vaccines also shows promise, with nearly 40% reductions in overall infant mortality (*21*, *22*, *52*). These successes clearly highlight the protective potential of neonatal and maternal immune components. Enhanced protection will likely require previously unexplored strategies that combine vaccination of mothers and their newborns to simultaneously stimulate pathogen-agnostic and pathogen-specific immunity (Fig. 2C). Physicians are instructed to first "do no harm." This instills a reflexive reluctance to deviate from the status quo. Unfortunately, the current status quo is that nearly half of under-age-5 mortality occurs in neonates, and a large fraction of these deaths are due to infection. Perhaps actively excluding pregnant mothers and newborns from vaccine research is inadvertently causing even more harm. The priority should be to protect these vulnerable populations through research, not from it.

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